

REMARKS/ARGUMENTS

Claim 14 has been canceled. Claims 9-13 are pending. Reconsideration is respectfully requested.

Applicants' representative wishes to thank Examiner Lambkin for the helpful and courteous interview of July 24, 2007. As a result of the discussion, it is believed that the issues in the case have been clarified and that the prosecution of the application has been materially advanced.

The present invention relates to a method of treating impaired gastric accommodation.

Claim Amendment

Claim 9 has been altered in form and amended to recite that the effect of improvement of the impairment of gastric accommodation in a subject is achieved by relaxation of the gastric fundus, which finds support in the specification at the bottom of page 2. Entry of the amendment is respectfully requested.

Rejection, 35 U.S.C. §102

Claims 9-13 stand rejected under 35 U.S.C. 102(b) as being anticipated by Nagasawa et al., U.S. Patent No. 5,981,557, Nagasawa et al, JP10-212271 (abstract) and Nakajima et al., J. Smooth Muscle Res. 36:69. The ground of rejection is respectfully traversed.

The Examiner states in her ground of rejection that, because the same compounds are used to treat the same symptoms of the gastric dysfunctions of nausea and bloating, the skilled artisan would use the compounds to treat, what the Examiner views as essentially the same disorders of gastric dysmotility and impaired gastric accommodation, with the known compound embodiments. However, as applicants will show in the discussion below, at the time of the present invention of an effective method of alleviating impaired gastric

accommodation, this condition had not been recognized for what it is in the international community. How then could the presently claimed method of alleviating impaired gastric accommodation have been obvious to those of skill in the art at the time the present invention was made?

Applicants emphasize firstly that they are not claiming methods of treating gastric dysmotility, bloating or nausea. Rather, applicants are claiming a method of treating impaired gastric accommodation, the effect of which treatment is the relaxation of the gastric fundus. Upon relaxation of the gastric fundus, favorable relief from early satiation is achieved. Applicants have been the first to recognize the claimed mode of action by the compound employed in the present method, as is evident from the fact that their discovery is disclosed in their priority application, filed April 8, 2002 and the subsequent international application that was filed April 8, 2003 from which the present application is derived, and by the fact that the functional gastrointestinal disorders had not even been classified based upon pathophysiological mechanisms until 2006! (see Rome III; GASTROENTEROLOGY, Vol 130, pp1466-1479, 2006) In other words, the present inventors had attained their invention long before the International Gastroenterological Association formalized gastrointestinal disorders into different classifications. Further, in view of the foregoing, applicants conclude that early satiation, which is a predominant symptom of the postprandial distress syndrome as shown in Rome III, is caused by impaired gastric accommodation of the gastric fundus, and not by dysfunction of gastric emptying of the gastric antrum.

For a more in depth understanding of the significant transition in understanding of the bases of functional dyspepsia over time, applicants enclosed copies of the publications known as Rome I, II and III with this document. More specifically, Rome I shows functional dyspepsia (FD) as classified into four sub-groups identified as 1) dysmotility-like dyspepsia, 2) ulcer-like dyspepsia, 3) reflux-like dyspepsia and 4) non-specific dyspepsia. (Rome criteria

originated from the Rome committee that was organized when an international meeting was held in Rome, Italy. In this meeting the committee's action focused on the irritable bowel syndrome.)

Rome II (1992) proposed a classification of functional dyspepsia (FD) into three sub groups identified as 1) dysmotility-like dyspepsia, 2) ulcer-like dyspepsia, and 3) non-specific dyspepsia. (Note: reflux-like dyspepsia for which no particular lesions are established as proven by endoscopic examination was categorized as a gastroesophageal reflux disease, and was categorized as a gastroesophageal reflux disease, and therefore excluded as a sub-group.)

The definition of FD was amended to specify that symptoms were intermittent or continuous for a period of at least twelve weeks over the past twelve months without identifying structural disease, and that no alleviation of the symptoms was achieved after defecation.

It had been observed that FD is linked to impaired gastric accommodation and disturbance of sensory function, as well as impaired gastric emptying, in the progress of research and validation therefor. However, impaired gastric accommodation and its associated symptoms were not specified by Rome II.

Rome III (2006) proposed that FD be classified into the two sub-groups as 1) postprandial distress syndrome, and 2) epigastric pain syndrome. Functional gastroduodenal disorders in the absence of any organic, systemic or metabolic diseases that were likely to explain their symptoms were classified in Category B. According to the general and comprehensive definition of FD categorized as B1, FD is associated with a symptom that originates from the gastroduodenal region, specifically epigastric burning, postprandial fullness or early satiation. Symptoms that have evidence of structural disease proven by

endoscopic examination were excluded. Rome III further established that the diagnostic criteria for the nine classifications described were fulfilled for the last three months with symptoms at least 6 months before diagnosis, the duration of which had decreased.

Functional dyspepsia was further subdivided into the two sub-groups of Postprandial Distress Syndrome and Epigastric Pain Syndrome. Postprandial Distress Syndrome is mainly associated with postprandial fullness or early satiation and Epigastric Pain Syndrome is mainly associated with epigastric pain or epigastric burning.

In summary, Rome I proposed subdivision on the basis of symptom clusters. However, the classifications had considerable overlap which resulted in limiting its value.

Rome II proposed subdivision based on predominant symptoms such as pain and discomfort and had the following disadvantages: i) difficulty in distinguishing pain from discomfort, ii) lack of acceptance of the term “predominant,” iii) many patients do not fit into any-subgroup, and iv) the lack of stability of symptoms even for a short period of time.

Rome (III) proposed that the FD be sub-classified into two categories of syndromes of postprandial distress and epigastric pain based on the pathophysiological mechanism of FD. It is noteworthy that the definition of FD was drastically changed to an entity characterized by the different syndromes.

The discussion above clearly establishes that functional gastrointestinal disorders had not been established on pathophysiological mechanisms until 2006, which is well after applicants’ discovery and claimed method of treating the gastric fundus as a means of alleviating an aspect of gastric distress.

At the time of the filing of what was to become the Nagasawa et al ‘557 patent, the diagnostic criteria for FD were not completely established, and there was no criterion for the

dysfunction of relaxing the gastric fundus after meals. Thus, the pathophysiological mechanism of the present invention is different from that of the reference. In Nagasawa et al FD is directed to motility disorders of the esophagus or the stomach. At that time, in general, irritable bowel syndrome was the major subject of the research of functional gastrointestinal disorders. Attention was also given to impaired gastric emptying as a cause of disease in the absence of any organic disease such as gastric ulcer, but associated with subjective symptoms such as indefinite complaint and gastric pain. Such a disease was simply evaluated as a “non-ulcer dyspepsia.”

It should be noted that impaired gastric emptying had been recognized as a pathophysiological mechanism of non-ulcer dyspepsia. In fact, various attempts had been made to develop therapeutic agents such as Itopride and Mosapride starting from the discovery of Prokinetics. However, no therapeutic agent was specifically targeted to improve impaired gastric accommodation.

The Rome committee has been mentioned above. This committee acted by focusing on irritable bowel syndrome. FD remained classified into the following subgroups: (1) dysmotility-like dyspepsia; (2) ulcer-like dyspepsia; (3) reflux-like dyspepsia and (4) non-specific dyspepsia. Dysmotility-like dyspepsia, which is mainly associated with postprandial fullness, is caused by delayed gastric emptying as a pathophysiological mechanism. In ulcer-like dyspepsia pain is a major complaint. Reflux-like dyspepsia (esophageal disorders) are associated with heartburn as a major complaint. Other symptoms that do not fit into the three subgroups are placed into the fourth category.

In light of this background, the disclosure of the Nagasawa et al patent is directed to a therapeutic agent that functions by promoting gastric emptying by enhancing gastric motility. On the other hand, the present invention has a much different basis. Research results for FD,

diagnosed according to the classifications of Rome II, were collected and recognized as syndromes that are associated with various symptoms therefore. Improvements in technology directed to the objective of establishing a new method for determining motility function have led to the findings of “impaired gastric accommodation” and “disturbance of sensory function.” In FD impaired gastric accommodation correlates significantly to early satiation. In the present invention, gastric accommodation, as a gastric motility function is a key for evaluating FD. Measurements of gastric accommodation by the Barostat method and the Scintigraphy method and such like have revealed that this physiological function is served to accommodate meals by relaxing the gastric fundus. (According to Tack et al, Gastroenterology, 1998, 115, pp 1346-1352; 40 % of dyspeptic patients have impaired gastric accommodation associated with early satiation.)

After the committee had defined the diagnostic criteria for FD in Rome II, rapid advances in research encouraged the committee to revise Rome II to the scope developed in Rome III in 2006. According to Rome III, at least one of the following conditions must exist in a diagnosis of FD: 1) bothersome postprandial fullness; 2) early satiation; 3) epigastric pain and 4) epigastric burning. Particularly notable is that early satiation significantly correlates with impaired gastric accommodation and is clearly defined as an essential factor in the diagnosis of FD. Thus, the present invention is directed to a therapeutic agent which relaxes the gastric fundus after a meal, thereby alleviating early satiation. It is therefore believed that the Nagasawa et al patent neither anticipates nor obviates the invention as claimed. Withdrawal of the rejection is respectfully requested.

The comments asserted above with respect to the Nagasawa et al, ‘557 patent apply equally as well to the Nagasawa et al, JP ‘271 reference which discloses the treatment of motion disorders of the gastrointestinal tract which include nausea and bloatedness (feeling of fullness of the abdomen). There is no teaching or suggestion of treating impaired gastric

accommodation in the reference. Accordingly, withdrawal of the rejection is respectfully requested.

The Nakajima et al publication describes the induction of “gastrointestinal prokinetic action” (abstract) and action which stimulates gastric motility (page 80). As pointed out above, gastric dysmotility is distinct from gastric accommodation. Even though the two conditions may give rise to the same or similar symptoms such as nausea and bloatedness, they nevertheless are different impairments involving different parts of the gastrointestinal system. Thus, the anticipatory ground of rejection is obviated and withdrawal of the rejection is respectfully requested.

Applicants again assert the evidence that has been presented of record in the response filed January 23, 2007 identified as Tack et al, Gut 52:1271.

The obviousness ground of rejection raised under 35 USC 103 is believed obviated by the comments made of record above which clearly assert that impaired gastric accommodation which is treated in the present invention is not the same thing as impaired gastric motility as discussed in the cited and applied prior art. Further, the references contain no disclosure which would motivate the skilled artisan from a basis of treating impaired gastric motility to the treatment of the fundus of the stomach in order to achieve improved gastric accommodation using much the same compound. Accordingly, withdrawal of the rejection is respectfully requested.

Applicants enclose an amendment of inventorship of the application under the provisions of 37 CFR 1.48(B1).

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Reply to Office Action of April 24, 2007

In view of the amendments and remarks above, the Applicants submit that this application is now in condition for allowance. An early notification to such effect is respectfully requested.

Respectfully submitted,

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